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Patent
Attorney's Docket No. 002010-680

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
Konradi, et al.	Confirmation No. 2073
Application No.: 09/910,702	Group Art Unit: 1646
Filed: July 20, 2001	Examiner: T. N. Truong
For: Alpha Amino Acid Derivatives-Inhibitors of Leukocyte Adhesion Mediated by VLA-4	

AMENDMENT AND REPLY TO OFFICE ACTION

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This Amendment and Reply is submitted in response to the Office Action mailed February 5, 2003. This Office Action set a three month period for response. This response is being filed on or before its current due date of May 5, 2003.

Please amend Claims 1, 2, 8-11, 13 and 17-21 and add new Claims 22-27 as follows:

A1

1. (Amended) A compound (Ia) or (Ib):

04/07/2003 DTESSEM1 00000010 09910702

01 FC:1202 1206.00 OP
02 FC:1203 280.00 OP

1684

Patent
Attorney's Docket No. 002010-680

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Konradi, et al.	)	Group Art Unit: 1624
	)	
Application No.: 09/910,702	)	Examiner: B. Kifle
	)	
Filed: July 20, 2001	)	Confirmation No.: 1280
	)	
For: ALPHA AMINO ACID DERIVATIVES-INHIBITORS OF LEUKOCYTE ADHESION MEDICATED BY VLA-4	)	

AMENDMENT/REPLY TRANSMITTAL LETTER

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Enclosed is a an Amendment and Reply in response to the Office Action, mailed on February 5, 2003, for the above-identified patent application.

[ ] A Petition for Extension of Time is also enclosed.

[ ] A Terminal Disclaimer and the [ ] $55.00 (2814) [ ] $110.00 (1814) fee due under 37 C.F.R. § 1.20(d) are also enclosed.

[ ] Also enclosed is/are _____.

[ ] Small entity status is hereby claimed.

[ ] Applicant(s) request continued examination under 37 C.F.R. § 1.114 and enclose the [ ] $375.00 (2801) [ ] $750.00 (1801) fee due under 37 C.F.R. § 1.17(e).

[ ] Applicant(s) previously submitted ___, on ___, for which continued examination is requested.

[ ] Applicant(s) request suspension of action by the Office until at least ___, which does not exceed three months from the filing of this RCE, in accordance with 37 C.F.R. § 1.103(c). The required fee under 37 C.F.R. § 1.17(i) is enclosed.

[ ] A Request for Entry and Consideration of Submission under 37 C.F.R. § 1.129(a) (1809/2809) is also enclosed.

[ ] No additional claim fee is required.

[X] An additional claim fee is required, and is calculated as shown below:

AMENDED CLAIMS					
	NO. OF CLAIMS	HIGHEST NO. OF CLAIMS PREVIOUSLY PAID FOR	EXTRA CLAIMS	RATE	ADDT'L FEE
Total Claims	154	MINUS 87 =	67	× $18.00 (1202) =	$1206.00
Independent Claims	1	MINUS 3 =	0	× $84.00 (1201) =	.00
If Amendment adds multiple dependent claims, add $280.00 (1203)					$280.00
Total Amendment Fee					$.00
If small entity status is claimed, subtract 50% of Total Amendment Fee					
TOTAL ADDITIONAL FEE DUE FOR THIS AMENDMENT					$1,486.00

[X] A claim fee in the amount of $ 1486.00 is enclosed.

[ ] Charge $_____ to Deposit Account No. 02-4800.

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17, 1.20(d) and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800. This paper is submitted in duplicate.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: Galina Yakovleva
Galina M. Yakovleva
Registration No. 47,192

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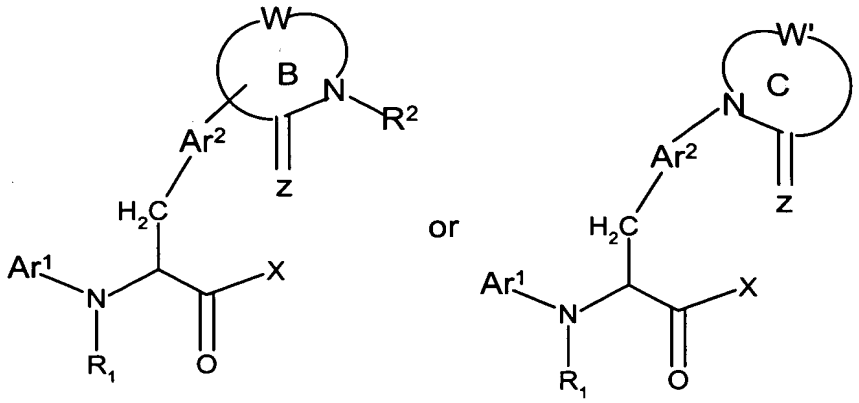
Date: April 1, 2003



(Ia) (Ib)

A1

wherein:

Ar^1 is an aryl, heteroaryl, cycloalkyl, or heterocyclic group wherein said aryl, heteroaryl, cycloalkyl, or heterocyclic group is optionally substituted, on any ring atom capable of substitution, with 1-3 substituents selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, substituted amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, cyano, halogen, hydroxyl, nitro, oxo, carboxyl, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR where each R is independently hydrogen or alkyl, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted

aryl, -NRS(O)$_2$-heteroaryl, -NRS(O)$_2$-substituted heteroaryl, -NRS(O)$_2$-heterocyclic, -NRS(O)$_2$-substituted heterocyclic, -NRS(O)$_2$-NR-alkyl, -NRS(O)$_2$-NR-substituted alkyl, -NRS(O)$_2$-NR-aryl, -NRS(O)$_2$-NR-substituted aryl, -NRS(O)$_2$-NR-heteroaryl, -NRS(O)$_2$-NR-substituted heteroaryl, -NRS(O)$_2$-NR-heterocyclic, -NRS(O)$_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, -N[S(O)$_2$-R′]$_2$ and -N[S(O)$_2$-NR′]$_2$ where each R′ is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

R^1 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

A1

Ar^2 is an aryl or heteroaryl group optionally substituted, in addition to ring B or C, with one or two substituent(s) selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, substituted alkoxy, acyloxy, amino, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, acylamino, aminoacyl, N-acyl-N-alkylamino, substituted N-acyl-N-alkylamino, (alkylsulfonyl)amino, substituted (alkylsulfonyl)amino, N-(alkylsulfonyl)-N-alkylamino, substituted N-(alkylsulfonyl)-N-alkylamino, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, cyano, acyl, substituted acyl, carboxy, substituted carboxy, thiol, alkylthio, substituted alkylthio, alkylsulfoxy, substituted alkylsulfoxy, alkylsulfonyl, and substituted alkylsulfonyl;

Z is -O- or -S-;

B is a group wherein W, together with -C(=Z)NR^2-, forms a saturated or unsaturated heterocyclic group containing 2 to 5 carbon atoms and 0 to 4 additional heteroatoms selected from the group consisting of nitrogen, oxygen, and -SO$_n$- (where n is 0 to 2) wherein said saturated or unsaturated heterocyclic group is optionally fused with one

or two ring(s) structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group to form a bi- or tri-fused ring system and further wherein said heterocyclic group and each of such ring structures are optionally substituted with 1 to 3 substituents selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, substituted alkoxy, acyloxy, substituted acyloxy, amino, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, acylamino, substituted acylamino, N-acyl-N-alkylamino, substituted N-acyl-N-alkylamino, alkylene dioxy, (alkylsulfonyl)amino, substituted (alkylsulfonyl)amino, N-(alkylsulfonyl)-N-alkylamino, substituted N-(alkylsulfonyl)-N-alkylamino, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, cyano, acyl, substituted acyl, carboxy, substituted carboxy, nitro, thiol, alkylthio, substituted alkylthio, alkylsulfoxy, substituted alkylsulfoxy, alkylsulfonyl, substituted alkylsulfonyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkenyloxy, substituted alkenyloxy;

A1

R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, and substituted cycloalkenyl;

C is a group wherein W', together with -C(=Z)N-, forms a saturated or unsaturated heterocyclic group containing 2 to 5 carbon atoms and 0 to 4 additional heteroatoms selected from the group consisting of nitrogen, oxygen, and $-SO_n-$ (where n is 0 to 2) wherein said saturated or unsaturated heterocyclic group is optionally fused with one or two ring(s) structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group to form a bi- or tri-fused ring system and further wherein said heterocyclic group and each of such ring structures are optionally substituted with 1 to 3 substituents selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, substituted alkoxy, alkylenedioxy, acyloxy, substituted acyloxy, amino, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, acylamino,

substituted acylamino, N-acyl-N-alkylamino, substituted N-acyl-N-alkylamino, (alkylsulfonyl)amino, substituted (alkylsulfonyl)amino, N-(alkylsulfonyl)-N-alkylamino, substituted N-(alkylsulfonyl)-N-alkylamino, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, cyano, nitro, acyl, substituted acyl, carboxy, substituted carboxy, thiol, alkylthio, substituted alkylthio, alkylsulfoxy, substituted alkylsulfoxy, alkylsulfonyl, substituted alkylsulfonyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

X is selected from the group consisting of hydroxyl, alkoxy, substituted alkoxy, alkenoxy, substituted alkenoxy, cycloalkoxy, substituted cycloalkoxy, cycloalkenoxy, substituted cycloalkenoxy, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy and -NR″R″ where each R″ is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

A1

and enantiomers, diasteromers or pharmaceutically acceptable salts thereof;

and further wherein the compound of Formula I has a binding affinity to VLA-4 as expressed by an IC_{50} of about 15μM or less.

2. (Amended) The compound of Claim 1 wherein (Ia), B is a group wherein W, together with -C(=Z)NR^2- where Z is -O-, forms an unsaturated heterocyclic group containing 2 to 4 carbon atoms and 0 to 2 additional nitrogen atoms and further wherein the unsaturated heterocyclic group is optionally substituted, in addition to the R^2 group, with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino.

A2

8. (Amended) The compound as in one of Claims 1 to 7 wherein Ar^2 is phenyl.

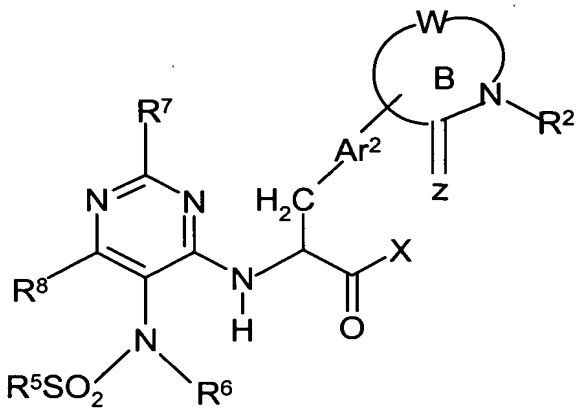
9. (Amended) The compound as in one of Claims 1 to 7 wherein X is hydroxyl and R^1 is hydrogen.

10. (Amended) The compound as in one of Claims 1 to 7 wherein Ar^2 is phenyl, X is hydroxyl and R^1 is hydrogen.

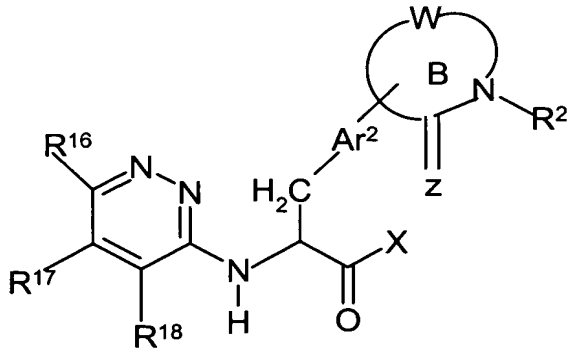
11. (Amended) The compound of Claim 1 wherein the compound has formula IIa, IIb, IIc, IId, or IIe:

A2

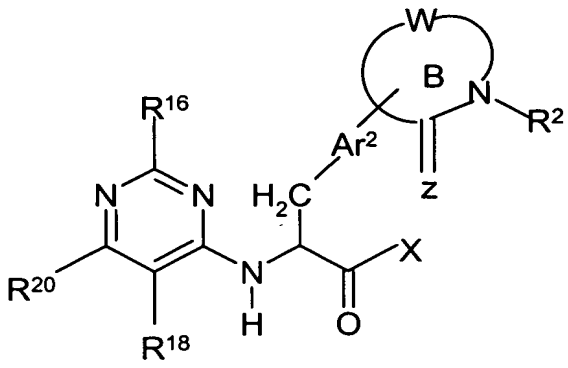
IIa



IIb

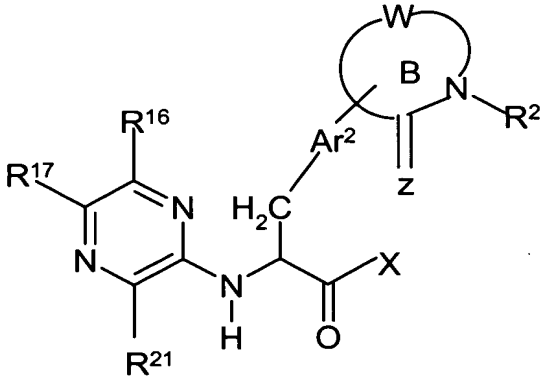


IIc

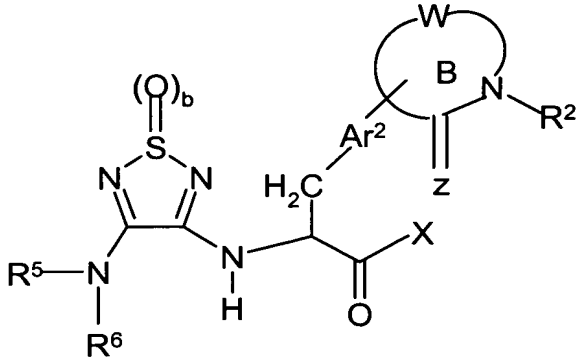


A2

IId



IIe



wherein

X is hydroxyl or alkoxy;

Ar^2 is an aryl or heteroaryl group optionally substituted, in addition to ring B, with one or two substituent(s) selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, substituted alkoxy, acyloxy, substituted acyloxy, amino, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, acylamino, substituted acylamino, N-acyl-N-alkylamino, substituted N-acyl-N-alkylamino, (alkylsulfonyl)amino, substituted (alkylsulfonyl)amino, N-(alkylsulfonyl)-N-alkylamino, substituted N-(alkylsulfonyl)-N-alkylamino, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, cyano, acyl, substituted acyl, carboxy, substituted carboxy, thiol, alkylthio, substituted alkylthio, alkylsulfoxy, substituted alkylsulfoxy, alkylsulfonyl, and substituted alkylsulfonyl;

A2

R^5 is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and -SO_2R^{10} where R^{10} is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

R^7 and R^8 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen;

R^{16} and R^{17} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl,

substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen; and

R^{18} is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

R^{20} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and halogen;

A2

R^{21} is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclic and substituted heterocyclic;

b is 1 or 2; and

B is a group wherein W, together with $-C(=Z)NR^2-$, forms a saturated or unsaturated heterocyclic group containing 2 to 5 carbon atoms and 0 to 4 additional heteroatoms selected from the group consisting of nitrogen, oxygen, and $-SO_n-$ (where n is 0 to 2) wherein said saturated or unsaturated heterocyclic group is optionally fused with one or two ring(s) structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group to form a bi- or tri-fused ring system and further wherein said heterocyclic group and each of such ring structures are optionally substituted with 1 to 3 substituents selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, substituted alkoxy, acyloxy, substituted acyloxy, amino, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, acylamino, substituted acylamino, N-acyl-N-alkylamino, substituted N-acyl-N-alkylamino, alkylene dioxy, (alkylsulfonyl)amino, substituted (alkylsulfonyl)amino, N-(alkylsulfonyl)-N-alkylamino, substituted N-(alkylsulfonyl)-N-alkylamino, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted

alkynyl, cyano, acyl, substituted acyl, carboxy, substituted carboxy, nitro, thiol, alkylthio, substituted alkylthio, alkylsulfoxy, substituted alkylsulfoxy, alkylsulfonyl, substituted alkylsulfonyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkenyloxy, substituted alkenyloxy;

A2

R^2 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, and substituted cycloalkenyl; and

and enantiomers, diastereomers or pharmaceutically acceptable salts thereof.

13. (Amended) The compound of Claim 11 wherein B is a group wherein W, together with $-C(=Z)NR^2-$ where Z is -O-, forms an unsaturated heterocyclic group containing 2 to 4 carbon atoms and 0 to 2 additional nitrogen atoms and further wherein the unsaturated heterocyclic group is optionally substituted, in addition to the R^2 group, with 1 or 2 substituents selected from the group consisting of alkyl, alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, halo, hydroxy, mono or dialkylamino.

A3

17. (Amended) The compound as in any one of Claims 11 to 16 wherein Ar^2 is phenyl.

18. (Amended) The compound as in any one of Claims 11 to 16 wherein X is hydroxyl and R^1 is hydrogen.

A4

19. (Amended) The compound as in any one of Claims 11 to 16 wherein Ar^2 is phenyl, X is hydroxyl and R^1 is hydrogen.

20. (Amended) A method for treating a disease mediated by VLA-4 in a patient, which method comprises administering a pharmaceutical composition comprising a

pharmaceutically acceptable carrier and a therapeutically effective amount of a compound as in any one of Claims 1-7 or 11-16.

A4

21. (Amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound as in any one of Claims 1-7 or 11-16.

22. (New) A method for treating a disease mediated by VLA-4 in a patient, which method comprises administering a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound as in any one of Claims 1-7 or 11-16 wherein Ar^2 is phenyl.

A5

23. (New) A method for treating a disease mediated by VLA-4 in a patient, which method comprises administering a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound as in any one of Claims 1-7 or 11-16 wherein X is hydroxyl and R^1 is hydrogen.

24. (New) A method for treating a disease mediated by VLA-4 in a patient, which method comprises administering a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound as in any one of Claims 1-7 or 11-16 wherein Ar^2 is phenyl, X is hydroxyl and R^1 is hydrogen.

25. (New) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound as in any one of Claims 1-7 or 11-16 wherein Ar^2 is phenyl.

26. (New) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound as in any one of Claims 1-7 or 11-16 wherein X is hydroxyl and R^1 is hydrogen.

AS

27. (New) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound as in any one of Claims 1-7 or 11-16 wherein Ar^2 is phenyl, X is hydroxyl and R^1 is hydrogen.